EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Level of evidence from Orphan Designation to EU Marketing Authorisation

EMA- EuropaBio Information Day
Orphan Medicinal Products
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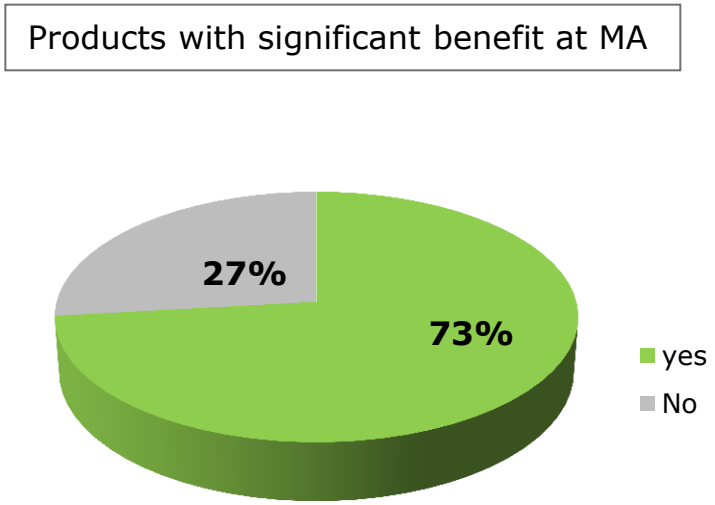
Orphan criteria

- **Prevalence/return on investment**
- **Seriousness:**
- (Medical plausibility)
- **Significant benefit:** the clinically relevant advantage or the major contribution to patient care that the product will bring to the management of the disease as compared to what already authorized (satisfactory) for the condition
- IF SATISFACTORY METHODS EXIST
- Based on assumptions at OD. Need of data at MA



Prevalence

- Conclusions based on info provided by the sponsor
- Difficult in case of subsets or conditions close to threshold
- Moving target
  - changes in classification (ALI and ARDS = ARDS)
  - better case definition/diagnostics (eosinophilic esophagitis)
  - increased population age and/or survival (renal cell carcinoma)
- Agreement may be missing in scientific community (e.g. complete vs. e.g. 5/10/15 years prevalence in some cancers)

Satisfactory methods = Comparators?

- **Satisfactory =** all authorized medicinal products (MP) for that condition (in at least 1 MS); non pharmacological treatments treatment (e.g. surgery, RT, diet) considered satisfactory in the standard of care of that condition

- **All what is satisfactory is a comparator or are there "relevant" comparators?**

- MP with same therapeutic indication/clinical use
- different comparators at OD and MA possible
- different comparators for different grounds/domains of significant benefit

Significant Benefit is assessed

1. at Orphan Designation
2. at Protocol Assistance (requested by the Sponsor)
3. at Marketing Authorisation
4. in case of ”Art. 8.2” (Market Exclusivity removal procedure)

Different level of evidence is required

Scientific aspects of SB: retrospective appraisal

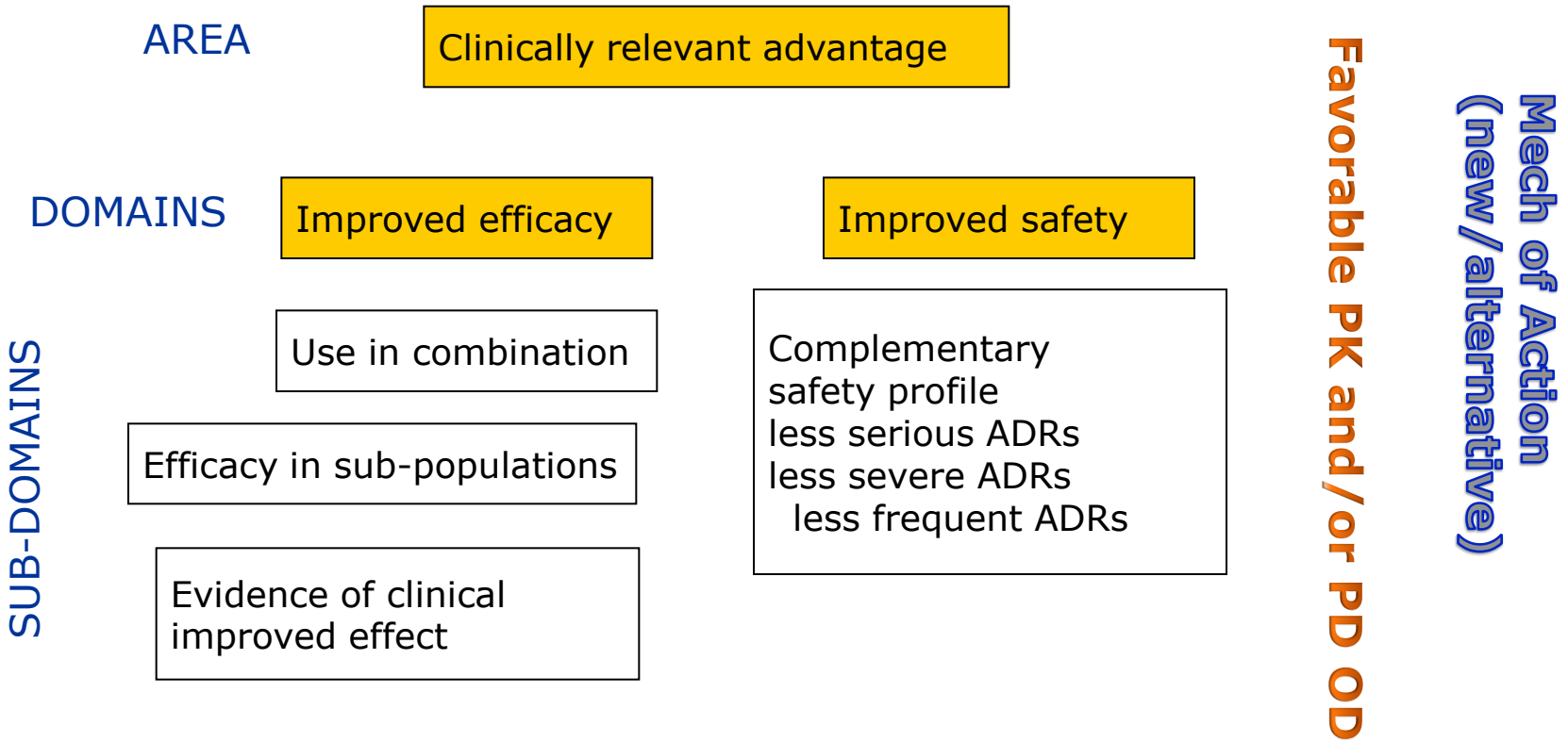
•Retrospective analysis of all authorized OMPs since 2000

•Review of COMP reports at OD and MA per each authorized OMP

•Identification of scientific concepts and of domains and sub-domains within the two main areas of SB

- Criteria for definition of domains and-sub-domains:
  - EMA/COMP/15893/2009 Recommendations
  - working experience of the COMP
  - sound scientific and pharmacological concepts

SB grounds (Retrospective analysis authorized OMPs)



Note: grounds are not mutually exclusive, i.e. one product can have more than one ground

SB grounds (Retrospective analysis authorized OMPs)

AREA

Major contribution to patient care

DOMAINS

Availability

Ease of use

SUB-DOMAINS

Improved availability from EU authorization

More convenient formulation/administration route

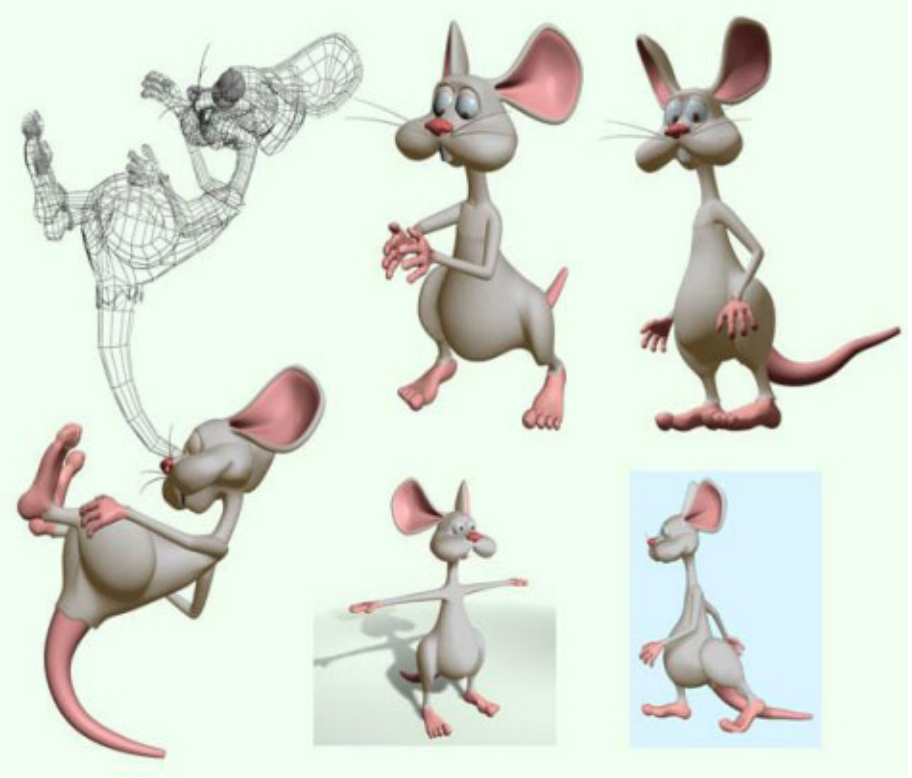
Shortage of supply

Dosing schedule

Favorable PK and/or PD OD

Significant benefit at the time of Orphan Designation

- Based on scientifically supported assumptions and hypotheses
- Usually evidence from good pharmacodynamic animal models (e.g. transgenic animals, knock-out animals, animals carrying specific mutations, etc.)
- Sometimes based on cell cultures experiments or "proof of principle" clinical data



How much evidence needed at OD?

- *in vitro* data sufficient? (no valid animal models; controversial animal models)
- animal models:
  - validity of the animal model
  - translational relevance of the findings
- clinical data (e.g. in most cancers and other frequently designated conditions preliminary clinical data increase likelihood of success)
- robustness" and clinical meaningfulness of early clinical data (e.g. case series; phase I/II data, etc)

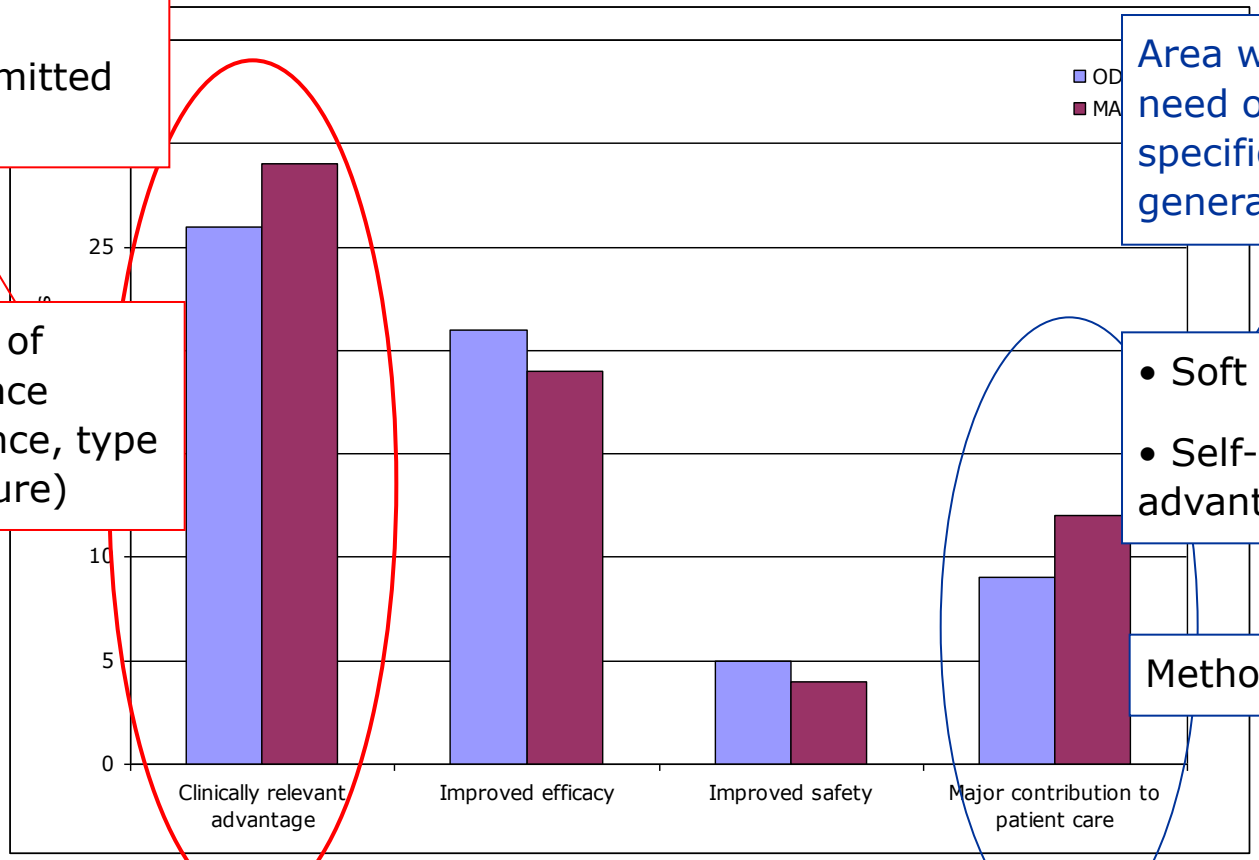
Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)

- Higher level of evidence required for review of orphan status at MA
- assumptions need to be confirmed with data (including MCPC)
- "*…..it has to be concrete and based on the data contained in the application for marketing authorisation and the arguments presented by the sponsor*"
- Increasing number of products = need of ad hoc data for SB
- Importance of protocol assistance

Main areas of significant benefit

Judgement on E&S at MA linked to evidence submitted to the CHMP

Variable level of clinical evidence (e.g. prevalence, type of MA procedure)



Area with highest need of data specifically generated for SB

- Soft endpoints
- Self-evident advantages

Methodology?

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Problems?

- 2-3 months additional PFS in cancer patients relapsing/refractory to previous treatments---clinical relevance?
- Quantification of "unquantifiable" endpoints/self-evident advantages? (e.g. better palatability, ease of use)
- Caveat when advantage linked to device
- Which use of indirect comparisons? (metanalysis, registry data, ect)
- Lack of "conditional" significant benefit in case of conditional approval

Workshop on methodology of significant benefit, EMA December 7, 2015

Thank you

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